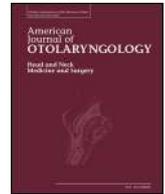




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Sleep disordered breathing in children with trisomy 13 and trisomy 18[☆]

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ABSTRACT

Purpose: While the prevalence of obstructive sleep apnea (OSA) is well documented in trisomy 21, there has been little published about the incidence in trisomy 13 (T13) and trisomy 18 (T18). Trisomies 13, 18, and 21 have overlapping clinical features that make patients prone to OSA. Because the literature regarding OSA in T13 and T18 children is limited, we performed a retrospective chart review to investigate the characteristics of these patients.

Methods: We reviewed the medical records of children with T13 or T18 seen at a single urban tertiary children's hospital for sleep disordered breathing from 1/1/10 to 5/1/18. Candidates were selected based on ICD-9 diagnosis and procedural codes.

Results: We identified 21 T18 patients that had documented symptoms of SDB, of which 3 were diagnosed with OSA, 11 had clinical SDB, and 7 had snoring. Of the T13 patients, 10 had documented symptoms of SDB, of which 1 patient was diagnosed with OSA, 7 with clinical SDB, and 2 with snoring. In both T13 and T18 patients, anatomical features included micrognathia/mandibular hypoplasia, small mouth/small airway, midface hypoplasia, abnormal/difficult airway, glossoptosis, hypotonia, and GERD. Endoscopic findings included laryngomalacia and/or tracheomalacia, adenoid and lingual tonsil hypertrophy, and inferior turbinate hypertrophy. Surgical interventions performed in T13 and T18 patients included adenoidectomy, lingual tonsillectomy, and tracheostomy. Of the 32 T13 and T18 patients, 15 had to be intubated for respiratory insufficiency.

Conclusion: The results of our study suggest that T13 and T18 patients are at increased risk for OSA due to common features found in this population. These findings indicate a need for otolaryngologist intervention to increase both survival and quality of life in this population.

1. Introduction

Trisomy 18 (T18) and trisomy 13 (T13) are the second and third most common viable autosomal trisomy syndromes, respectively, after trisomy 21 [1–3]. While the prevalence of obstructive sleep apnea (OSA) and sleep disordered breathing (SDB) is well documented in trisomy 21, with reported prevalence rates as high as 80% in the pediatric population, there has been little published about OSA in T13 and T18 [4,5]. Trisomies 13, 18, and 21 have overlapping clinical features that can make these patients particularly prone to OSA, including central hypotonia, craniofacial defects, and gastroesophageal reflux [1,6–8].

Trisomy 18, known as Edwards syndrome, occurs in approximately

1 in 2500 pregnancies [2,9]. Trisomy 13, known as Patau syndrome, occurs in approximately 1 in 6400 pregnancies [2,9]. Both trisomy 13 and 18 are most commonly caused by maternal meiotic non-disjunction, and incidence of non-disjunction increases as maternal age increases [7,10]. From 1973 to 2006, the percentage of women between ages of 35 and 39 years becoming pregnant for the first time increased six-fold, and there was a four-fold increase for women aged 40 to 44 years [11]. An increase in the rates of T13 and T18 can be attributed to these factors as well as increased prenatal screening [11]. The majority of cases are now diagnosed in the prenatal period [12].

Trisomy 18 most often affects the cardiac, musculoskeletal, and nervous systems as well as craniofacial and abdominal development [1]. Typical craniofacial features include microcephaly, a narrow oral

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opening, micrognathia, and a narrow palatal arch [1,12]. Multi-systemic abnormalities are also seen in Trisomy 13. Trisomy 13 most often presents with CNS anomalies, midline facial defects, cleft lip and palate, cardiac defects, and polydactyly [2,3]. Additionally, the presence of laryngomalacia and gastroesophageal reflux are common findings in both T13 and T18 infants [8]. Cardiac failure, central apnea, and respiratory insufficiency are the most common causes of death in these patients [2].

Trisomies 13 and 18 have been historically considered incompatible with life, but survival varies widely based on genotype, phenotype, and the interventions undertaken [9,11]. Notably, T18 is not listed as an example of a condition for which resuscitation is not indicated in the neonatal resuscitation guidelines from the American Academy of Pediatrics [12]. For trisomy 18 and 13 the median survival is 6–14 days and 8.5–10 days, respectively, and only 5–10% of patients survive beyond one year [2,9]. Additionally, females with T18 are more likely to survive [12]. Fetal loss is more common for male fetuses, and amongst those born alive, females have a higher rate of survival compared to males [12]. These statistics, though, have begun to change with the advent of aggressive interventions in this population, and there are reports of patients living into their teens [1,2,13]. A recent study estimated one year survival for trisomy 18 to be as high as 25% for infants that received major interventions [12]. For those patients that survive the first year of life, the survival rate at 5 years is 84% for trisomy 13 and 91% for trisomy 18 [14].

While the level of care provided to T13 and T18 children remains a controversial topic, the number of procedures in this population has increased over time [9,14]. Otolaryngologists have a major role to play in caring for T13 and T18 patients, as a study by Nelson et al. showed that ear, nose, and throat procedures were the most common type of surgical intervention in T13 patients [2,15]. Another study found that 16.7% of procedures performed in the T13 and T18 population were otolaryngologic, with 25% of those being performed on the airway [2]. As more of these patients become surgical candidates, it is important to understand the unique needs of this population [2]. Because of the lack of publications on OSA/SDB in T13 and T18 children, we performed a retrospective chart review to investigate the incidence and characteristics of these patients.

2. Materials and methods

We reviewed the medical records of children with T13 or T18 seen at a single urban tertiary children's hospital from 1/1/10 to 5/1/18. Candidates were selected based on ICD-9 diagnosis and procedural codes. We defined SDB as a range from symptoms of snoring to polysomnographic diagnosed obstructive sleep apnea. Clinical SDB was defined as nighttime snoring with evidence of pausing, gasping, and snoring was defined as nighttime snoring without the obstructive features. Participants included all patients with a diagnosis of T13 or T18. Exclusion criteria included children without a diagnosis of T13 or T18 and children that expired in the neonatal period who did not allow for adequate clinical evaluation for sleep disordered breathing. IRB approval was obtained from the UCSD IRB.

3. Results

3.1. Trisomy 18

The chart review identified 47 patients with T18, of which 21 had documented symptoms of SDB. The age range was 4 months to 23 years-old, with 13 females and 8 males. Four patients expired at ages 4 months, 7 months, 8 years, and 15 years-old. Comorbidities included 1 patient with Klippel-Feil syndrome and 1 patient with Cerebral Palsy.

Six patients had successful polysomnography and 3 were diagnosed with OSA, 11 had clinical SDB, and 7 with snoring (Table 1). A sleep study was ordered for 10 patients with only 6 successfully completing

Table 1

Number of T13 and T18 patients with OSA, SDB, or snoring.

	T18 patients	T13 patients
Total patients	47	19
Patients with OSA	3	1
Patients with clinical SDB	11	7
Patients with snoring	7	2

the study. Of the 6 with a completed sleep study, 3 had OSA which was moderate in severity (mean AHI 6.83 and mean O2 nadir 84%) and 3 had primary snoring (Table 2). Three patients were fit for positive airway pressure (PAP) therapy.

Documented anatomical features included 8 patients with micrognathia or mandibular hypoplasia, 7 with a small mouth or small airway, 2 with midface hypoplasia, 8 with an abnormal or difficult airway, 1 with glossoptosis, 12 with hypotonia, and 1 with GERD (Fig. 1).

Six patients underwent endoscopic airway assessments with nasopharyngolaryngoscopy, and direct laryngoscopy and bronchoscopy. Endoscopic findings included 3 patients with laryngomalacia and tracheomalacia, 1 patient with adenoid and lingual tonsil hypertrophy, and 1 patient with inferior turbinate hypertrophy (Fig. 1).

Surgical interventions performed included 1 patient undergoing adenoidectomy and lingual tonsillectomy, another obtaining a tracheostomy, and another with an adenoidectomy only. Nine patients had to be intubated for respiratory insufficiency, and 1 was recommended intubation but parents elected not to proceed. The respiratory insufficiency resulted in 1 patient being dependent on PAP therapy (Table 3).

3.2. Trisomy 13

Nineteen patients were identified with T13, of which 10 had documented symptoms of SDB. The age range was 8 weeks to 20 years-old, with 7 females and 3 males. 2 patients had expired at 8 weeks 11 years-old. Comorbidities included 1 patient with Lennox-Gastaut syndrome.

One patient was diagnosed with OSA, seven with clinical SDB, and two with snoring. One patient had successful polysomnography and was diagnosed with OSA, 7 had clinical SDB, and 2 had snoring (Table 1). A sleep study was ordered for 5 patients with only 1 successfully completing the study, which resulted in the need for nighttime oxygen.

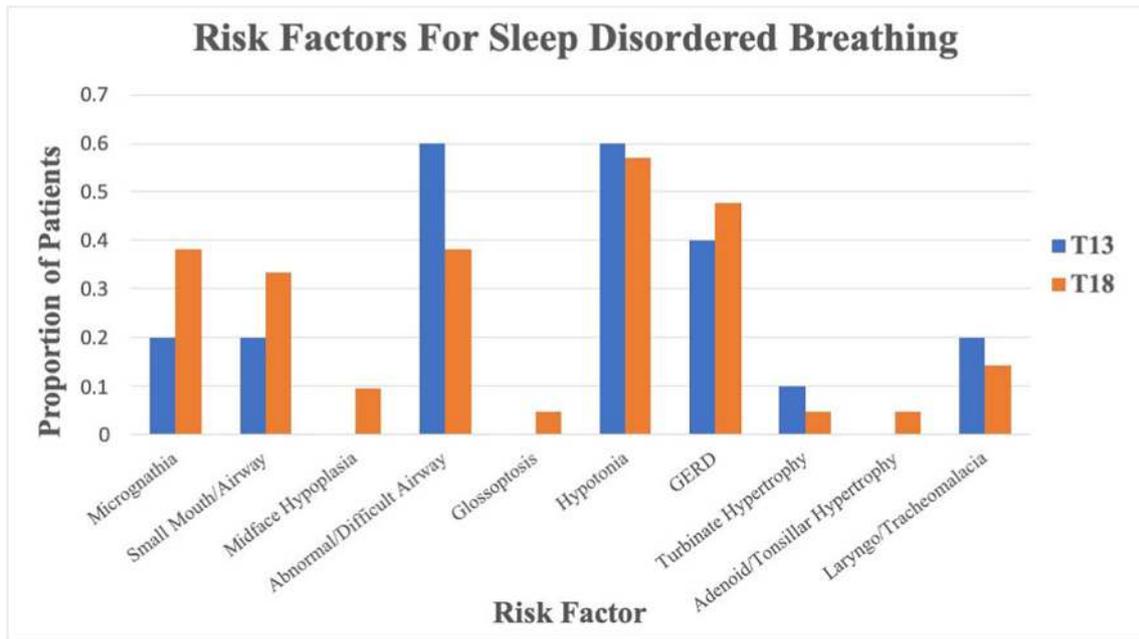
Documented anatomical features include 2 with micrognathia or mandibular hypoplasia, 2 with a small mouth or small airway, 6 with an abnormal or difficult airway, 6 with hypotonia, and 4 with GERD (Fig. 1). Four patients underwent endoscopic airway assessments with nasopharyngolaryngoscopy, and direct laryngoscopy and bronchoscopy. Endoscopic findings included 2 patients with tracheomalacia, 1 with laryngomalacia, and 1 patient with inferior turbinate hypertrophy (Fig. 1). Surgical interventions performed included 2 tracheostomies. Six patients had to be intubated for respiratory insufficiency, and 2 patients were PAP dependent, one of which was eventually weaned off PAP therapy (Table 3).

4. Discussion

SDB is an umbrella term which encompasses a spectrum of disease ranging from snoring to polysomnography confirmed obstructive sleep apnea [16]. OSA in children has a long list of sequelae that can negatively impact quality of life and cognitive function [17]. In our study, we found that 52.63% of T13 patients and 44.68% of T18 patients had evidence of SDB, significantly higher than the 1–4% prevalence in non-syndromic children (Fig. 2) [5]. Amongst the T13 and T18 participants,

Table 2Mean AHI, O₂ nadir, TST O₂ < 90%, TST ETCO₂ > 50 mmHg, and peak ETCO₂ recorded on overnight polysomnography in T18 and T13 patients.

	T18 overnight polysomnography N = 6 (SD)	T13 overnight polysomnography N = 1
Mean AHI	3.82 (3.46)	0.15
Mean O ₂ nadir	87% (0.05)	82%
Mean TST O ₂ < 90%	0.27% (0.52)	2.2
Mean TST ETCO ₂ > 50 mmHg	1.11% (2.64)	0
Mean Peak ETCO ₂	48.6 (5.14)	43 mmHg

**Fig. 1.** Risk factors found in T18 and T13 patients.**Table 3**

Incidence of airway surgery and respiratory insufficiency in T18 and T13 patients.

	T18	T13
Adenoidectomy	2	0
Lingual tonsillectomy	1	0
Tracheostomy	1	2
Intubated for respiratory insufficiency	9	6
PAP dependent	1	2 ^a

^a 1 patient was later weaned off PAP therapy.

there was documented maxillary hypoplasia (T13 = 20%, T18 = 38.1%), small mouth or airway (T13 = 20%, T18 = 33.3%), hypotonia (T13 = 60%, T18 = 57.1%), gastroesophageal reflux (T13 = 40%, T18 = 47.6%), and laryngomalacia (T13 = 20%, T18 = 14.3%). Additionally, midface hypoplasia (T18 = 9.5%), glossoptosis (T18 = 4.8%), and adenotonsillar hypertrophy (T18 = 4.8%) were present in the T18 population (Fig. 1).

OSA is well ascribed in T21 patients due to craniofacial abnormalities, alterations in oral musculature development, and hypotonia [6]. Specifically, midface and maxillary hypoplasia, microstomia, abnormally small upper airway, adenoid and tonsillar hypertrophy, glossoptosis, hypotonia, and laryngomalacia play a role [4,5,18]. Additionally, gastroesophageal reflux, which can lead to the inflammation and obstruction of the upper airway, is common in the T21 population [18]. Estimates of the prevalence of OSA in T21 patients ranges from 30% to 80% [6]. These overlapping clinical features place T21, T18, and T13 patients at a higher risk for SDB.

The gold-standard diagnostic procedure for OSA is

polysomnography (PSG). Accordingly, it is recommended that all T21 patients receive a PSG between the ages of 3 and 4, but no such recommendation has been established for T13 and T18 patients [4]. Given the results of our study, the overlapping clinical features and prevalence of SDB in T13 and T18 patients may be similar to T21. PSG, though, is a limited resource, and in this study we found that it can be difficult to obtain in this population due to fragile health status and patient intolerance of overnight monitoring. While many of our study participants were recommended or ordered a sleep study (T13 = 50%, T18 = 47.6%), few were able to complete the sleep study (T13 = 10%, T18 = 28.6%). Some reasons were documented, such as the child would not sleep or was too sick to complete the study, but many were not. The decision to pursue a sleep study is also subject to parent's and clinician's goals of care for the child, which ranged from intense intervention to palliative care. PAP therapy can be difficult for this patient population to tolerate, as noted in this study with one T13 patient whose parent noted intolerance of the PAP device while the other tolerated it.

A systematic review of the efficacy of adenotonsillectomy in T21 patients found that the surgery it is rarely curative, but on average decreases the AHI by about 51% [19]. Options for treating residual OSA include PAP, additional surgery, or tracheostomy. If surgery is to be pursued in a patient with T13 and T18, it is important to note that these patients can be difficult to manage. Many were documented to have an abnormal, small, or difficult airway (T13 = 70%, T18 = 42.9%). Additionally, many patients that underwent surgery remained intubated for one to ten days after surgery. Several failed extubation on numerous occasions. It is interesting to note that in contrast to T21, who often have tonsillar hypertrophy and undergo tonsillectomy, none of the T18 or T13 patients were noted to have tonsillar hypertrophy or obtained a

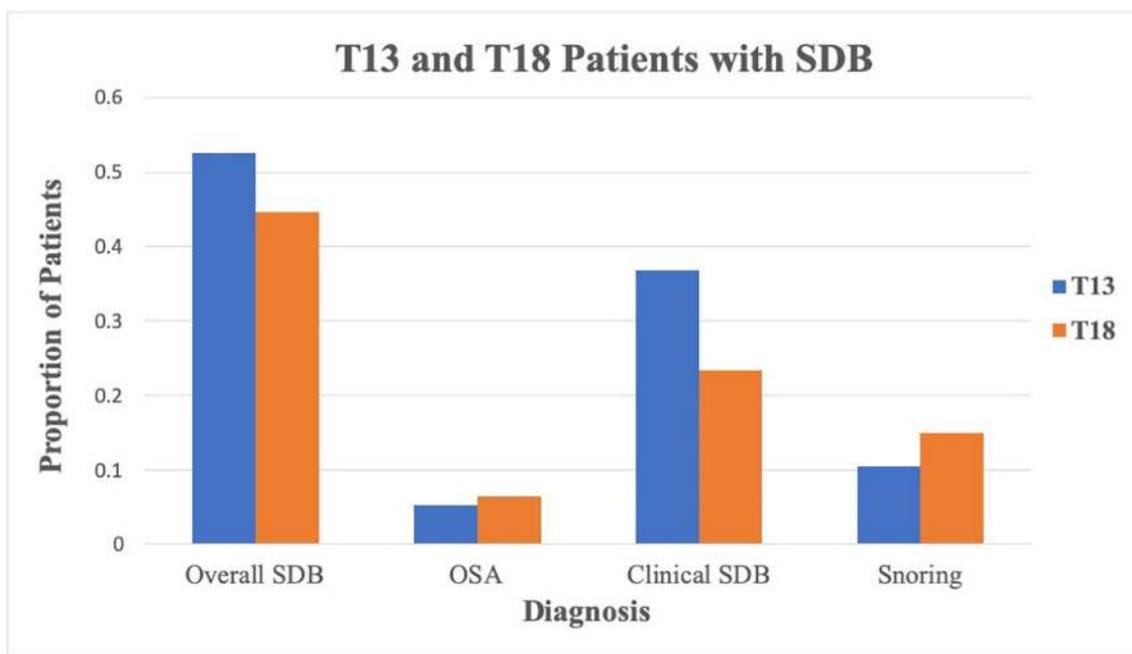


Fig. 2. Proportion of T18 and T13 patients with OSA, SDB, and snoring.

tonsillectomy.

Limitations of this study include its retrospective study design, as our results were dependent on what was documented. For example, we based our diagnoses of SDB on clinically noted symptoms, and providers with different priorities may have failed to document certain details. Many of our outcomes were subjective, and subject to differences in practice and opinion. For this patient population, there was not a focus on routinely obtaining sleep studies. Many sleep studies could not be completed, and this limited our ability to get a clear picture of the severity of OSA present. Additionally, these patients were managed heterogeneously. The extent of intervention depended on the health of the child and the desires of the caregivers. While further therapy may have been indicated, other considerations may have forestalled their implementation. Finally, our study was conducted at a single center and the sample size was small, limiting the generalizability of our findings.

5. Conclusion

In this study, we found that patients with T18 and T13 have clinical features that put them at higher risk for SDB. Based on our findings, we suspect that overall, OSA in T18 and T13 patients is underdiagnosed. Clinicians treating these patients should have a low threshold for screening this population. These patients may be difficult to treat, as many are fragile and do not tolerate diagnostic studies such as polysomnography and PAP therapy. This is the first study investigating SDB in T18 and T13 and provides a foundation of evidence as to why clinicians should be suspicious of SDB in this population. Optimizing the care provided to these children remains a controversial topic. As more T18 and T13 patients become surgical candidates, physicians may best serve the needs of these children by guiding practices based on available evidence. The number of procedures conducted in this population has increased over time, however the risks of surgical intervention needs to be considered very carefully as this fragile patient population often takes a long time to recover often resulting in extended ICU and hospital stays. The present study provides an initial foundation for future clinical decision making.

Declaration of competing interest

None.

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